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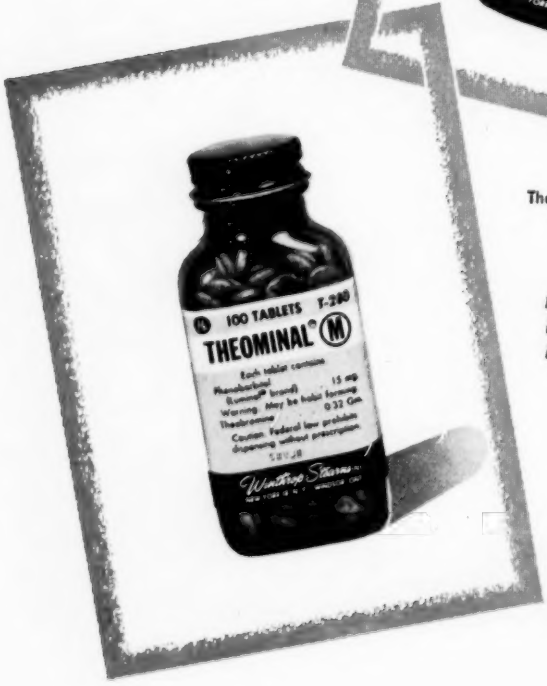

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*Kuhn, H. S.: Tr. Am. Acad. Ophth., p. 432, (March-April) 1951.

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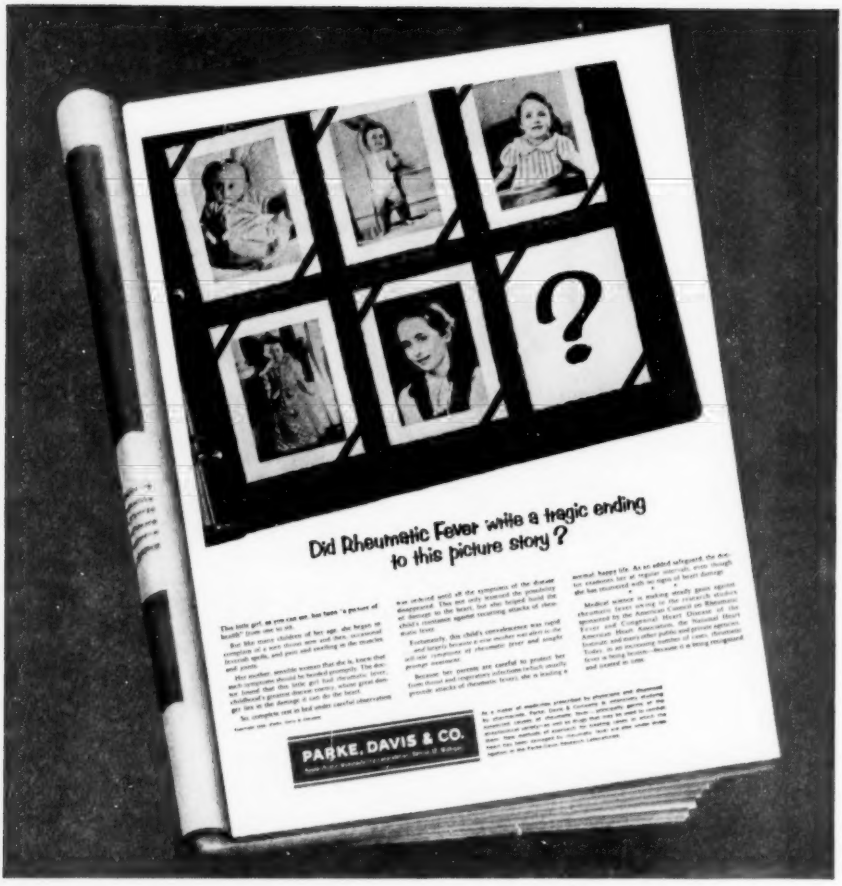

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EDITORIAL

AT LONG LAST

WE commend the action of the American Medical Association in the decision not to accept in its publications further advertising of tobacco and its products. For a number of years it has been an obvious fact that smoking is detrimental to health. Year after year the evidence has continued to pile up until the medical profession could no longer ignore it. This was particularly true in view of the several papers specifically relating the increased incidence of lung cancer with cigarette smoking. That there is such a causal relationship seems irrefutable in spite of certain efforts made by those with a financial interest at stake to minimize its importance or to question the validity of the evidence.

Lung cancer is not the only possible harmful effect of smoking. Cancer of the lip from pipe smoking is common and leukoplakia, a precancerous lesion of the oral mucosa, is found among many smokers. The unfavorable effect of smoking on patients with peptic ulcer is well established, as is its effect in impairing coronary circulation and in peripheral vascular disease. It is said that certain of the peripheral vascular diseases such as Raynaud's disease and Buerger's disease are much more common in heavy smokers than in others and some authorities even go so far as to indict smoking as a primary etiologic factor in these.

Were the cause of all these maladies anything less popular than smoking there would be legislation directed against it, just as there is against the use of morphine and cocaine. This actually was the case in the early days when tobacco smoking was first introduced in Europe, but as more and more people became addicted to the use of this poison it became generally accepted socially. Were we to make morphine easily available and spend millions of dollars annually to encourage people to use it we could in time make this habit just as popular and just as widely accepted. After all there is nothing more "normal" about the use of tobacco than the use of opium or coca leaves. Nicotine is not an essential metabolite and there is no evi-

dence to show that it serves any useful purpose in human metabolism except in the addict. The chewing of coca leaves as practiced in certain areas of South America is considered in these areas just as essential to the peoples' happiness and well being as tobacco smoking is here. It is amusing to read of current attempts made in the United Nations through W. H. O. to stamp out this practice of chewing coca leaves. While it surely should not be encouraged it is doubtful whether any better case can be made against it than can be made against tobacco if we adhere strictly to logic without the influence of public opinion. To the worker in the high Andes who chews coca leaves it would seem much more sensible to ban the use of tobacco. Is it not true that what most of us consider the worst vices are those which the other fellow has and we ourselves do not enjoy?

The worst part about the tobacco habit is the insidious and pervasive efforts to encourage new addicts. Millions are spent annually in advertising its products. The most glamorous young women and the most masculine of men are hired to impress the great American public with tobacco's joys and pleasures. Our children during their early impressionable years are convinced that the non-smoker is certain to be an "ugly duckling" and a social outcast. Even though the initial experience of smoking is most distasteful and unpleasant they persist in their unconscious drive to match as near as possible their ideal. It is no wonder that most adolescents begin smoking in their early teens. Once converted to the pleasure and necessity of satisfying their addiction they then can be listed as ready customers for life. If this is not exploitation of youth how else can it best be described?

We predict that the bad publicity current on the use of tobacco will cause the industry great concern and lead to counter measures of no small moment. With its size and wealth we can expect great things to come forth. In spite of all counter claims and counter measures what indeed is a better program than trying to discourage young people from acquiring the habit? Even the confirmed smoker if he is honest will urge his own son to forego the initial impulse to try smoking. While he must continue himself, the logic behind the argument not to smoke is inescapable. There is, even more, the lurking suspicion in even the most inveterate smoker that it does him harm. This he usually will not admit, for to do so would be an admission of irrational behavior.

To expect a mass movement in the direction of giving up tobacco is expecting too much. We in the health professions, however, have the moral and professional obligation to present the truth about smoking to the public and not become a party to the misrepresentations of those who sell tobacco products.

L. F. Tice

PROLONGATION OF ACTION OF HEPARIN BY PHOSPHORYLATED HESPERIDIN

By J. M. Beiler, R. Brendel and Gustav J. Martin *

THE chief detriment to the clinical use of heparin as an anticoagulant is its evanescent action. Efforts have been made to overcome this difficulty by the administration of heparin with substances which would tend to create a depot effect. Some of the combinations tried have been Pitkin's menstruum (1), beeswax (2), ephedrine and adrenalin (3, 4), peanut oil-beeswax (5), Gelatin-dextrose mixtures (6), and procaine or butocaine (7).

Phosphorylated hesperidin has been demonstrated to be an effective inhibitor of hyaluronidase both in vitro (8) and in vivo (9). This fact combined with the knowledge that hyaluronidase facilitates the absorption of fluids and drugs when administered by hypodermoclysis (10) led to the assumption that an inhibitor of this enzyme might produce a depot effect. The hypothesis has been tested and found correct.

Experimental and Results

The heparin used had a labelled potency of 107 units/mg. Cardiac blood was used for determination of clotting times; 0.8 cc. of blood was introduced into a test-tube of 9 mm. diameter and the time at which the blood ceased to flow on inversion of the tube was taken as the clotting time.

Results are presented in Tables I and II. All figures are average for 5 animals. Because of the impracticability of taking repeated blood samples from rats different groups of animals were used at each time interval. The same groups of rabbits were used throughout. Dosage of heparin used for the rats intramuscularly was 30 mg./k in 0.5 cc. of solution; intravenously, 10 mg./k in the same volume. In the rabbits the lowest dosages were used which would give consistent responses in different individuals of the group; these were found to be 15 mg./k intramuscularly and 4 mg./k I. V. In each case these dosages were administered in 1 cc. of solution. Gelatin where used was at 15% concentration, phosphorylated hesperidin at 4%.

* Research Laboratories, The National Drug Company, Philadelphia, Pennsylvania.

TABLE I

EFFECT OF PHOSPHORYLATED HESPERIDIN ON DURATION OF ACTION OF HEPARIN IN RATS

Time (hrs.)	Mode of Injection	Heparin & Saline	Heparin & Phos. Hesp.	Heparin & Phos. Hesp. & Gelatin	Heparin & Gelatin	Phos. Hesp.
Control		1'46"	2'03"	1'54"	2'00"	2'13"
1	I.M.	19'26"	7'52"	3'35"	3'29"	1'58"
2	"	*N.C.	12'10"	4'35"	4'18"	1'45"
3	"	N.C.	12'43"	17'20"	13'72"	1'55"
5	"	N.C.	18'50"	16'40"	15'46"	1'37"
6	"	N.C.	38'16"	33'30"	37'00"	2'16"
18	"	2'35"	9'04"	10'31"	8'00"	——
22	"	2'13"	5'12"	7'32"	4'00"	2'56"
Control		2'14"	1'37"			2'45"
1	I.V.	N.C.	N.C.			2'37"
2	"	7'36"	N.C.			2'43"
3	"	3'42"	70'00"			2'26"
4	"	3'42"	17'44"			2'42"
5	"	1'38"	3'12"			2'09"
6	"	1'49"	2'16"			1'47"

* N.C.—No clot for 2 hours.

TABLE II

EFFECT OF PHOSPHORYLATED HESPERIDIN ON DURATION OF ACTION OF HEPARIN IN RABBITS

Time (hrs.)	Mode of Injection	Heparin & Saline	Heparin & Phos. Hesp.	Heparin & Phos. Hesp. & Gelatin	Heparin & Gelatin	Phos. Hesp.	Control
0	I.M.	3'45"	3'23"	3'52"	3'26"	3'47"	3'40"
1	"	8'14"	3'47"	3'58"	3'58"	3'32"	3'51"
2	"	66'00"	5'43"	5'20"	58'00"	3'50"	3'23"
3	"	*N.C.	6'18"	6'27"	N.C.	3'16"	3'15"
4	"	15'00"	8'05"	7'35"	8'40"	3'22"	2'48"
5	"	5'27"	6'10"	6'23"	6'03"	3'19"	3'05"
0	I.V.	3'29"	3'16"	3'46"	3'25"	3'22"	3'45"
0.5	"	23'00"	38'00"	36'00"	17'00"	2'58"	3'31"
1	"	14'00"	18'00"	16'00"	10'00"	3'15"	3'30"
2	"	6'24"	5'36"	13'00"	3'24"	3'33"	2'59"
3	"	3'54"	2'58"	3'46"	——	3'14"	3'15"

*N.C.—No clot for 2 hours.

The results show clearly that phosphorylated hesperidin given intramuscularly with heparin will delay the absorption from the site of injection in both rats and rabbits, cutting down on the peak and giving in general a smoother and more consistent effect on clotting over a period of time. In rats, where higher doses of heparin were used than in the rabbits, increase in the duration of action of the heparin is also demonstrated. Gelatin was used as a standard heparin depot material. The figures show that on intramuscular injection the effect exerted by phosphorylated hesperidin alone is at least as great as that exerted by phosphorylated hesperidin plus gelatin or by gelatin alone.

Phosphorylated hesperidin has been shown to decrease capillary permeability, and to inhibit passage of dyes through the capillary wall (9). It was therefore felt that it might increase the duration of action of heparin on intravenous administration. This was found to be the case. The figures obtained with both rats and rabbits show that the effect on blood clotting of intravenously administered heparin remains high for an appreciably longer period when phosphorylated hesperidin is administered simultaneously. As might be expected, intravenously administered gelatin has no effect on the action of heparin.

The results provide few clues as to the mechanism of action. The fact that effects are obtained on both intramuscular and intravenous administration would make it appear that the phosphorylated hesperidin causes a decrease in cell permeability, presumably through inhibition of hyaluronidase. Phosphorylated hesperidin itself has no effect on blood clotting, either in vitro or in vivo (11). The possibility of clinical utility is enhanced by the fact that both intramuscular and intravenous effect can be shown. Further, the decreased rate of absorption and lowered peaking effect of heparin when it is given intramuscularly with phosphorylated hesperidin might well permit safe clinical use of heparin concentrations high enough to assure a long duration of action and a more nearly uniform effect.

Summary

Phosphorylated hesperidin has been shown to decrease the rate of absorption and the duration of action of intramuscularly administered heparin, and to increase the duration of action of intravenously administered heparin. Rats and rabbits were used as experimental animals.

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A REVIEW OF PRESERVATIVES USED IN PARENTERALS

By Edward A. Hartshorn *

THE use of parenterals dates back to 1831, with the first modern syringe being used in 1853 (1). Sometime in the period between these two dates the use of preservatives in parenterals was first tried.

A "preservative" in the layman's dictionary is a substance "having the power to preserve" (2), while preserve means "to protect, save or keep from decaying." A definition directed more to our subject would be: "a substance or substances used to maintain sterility or preserve activity during storage" (3). These definitions include not only bacteriostatic agents but also stabilizers. The term "parenteral" comes from the Greek language meaning outside of the intestinal tract (4). Its present meaning is a subcutaneous, intravenous or intramuscular injection.

The historical progress of preservatives, at least in England, runs something like this:

1885—camphor water

1895—0.15% salicylic acid and 1.0% phenol

1932—0.5% phenol became the yard-stick of bacteriostasis with 0.5% cresol and 0.5% chlorobutanol being used.

1938—the British Pharmacopoeia included monographs for the following preservative agents:

phenol	benzyl alcohol
cresol	phenylmercuric nitrate
chlorbutol	chlorocresol

Not listed are the popular parahydroxybenzoic acid esters and thimerosal. Although the above list dates back to 1938, there has appeared no preservative of note in recent years other than those two agents mentioned above.

Gershenfeld and Perlstein (5) listed the characteristics of the ideal preservative. This list is quoted frequently and many manu-

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facturers of preservatives try to sell their products by showing that their preservatives meet all of these standards, which are:

1. It must be effective against all types of micro-organisms causing decomposition.
2. It must be soluble in the concentration used.
3. It must be compatible, must not alter the character of the preparation as far as objectionable odor, color, taste, etc., and it must be practically neutral so that it will not alter the pH of the preparation.
4. It must not be toxic when used and in the concentration employed.
5. The cost of the preservative should not increase the price of the preparation to any marked extent.
6. The developed inhibiting effect must be lasting and therefore it may not be possible to depend on volatile substances, the effects of which disappear after evaporation.

Jones (6) lists some of the preservatives in groups, and gives the minimum concentration of each necessary for effective activity, and the maximum concentration allowable for safety (see Table 1).

TABLE 1

Group	Agent	Min. Conc. %	Max. Conc. %
A. Phenolic			
	Phenol	0.2	0.5
	Cresol	0.15	0.4
	n-butyl-p-hydroxybenzoate	0.01	
B. Neutral			
	Cholorobutanol	0.3	0.5
	Benzyl Alcohol	2.0	5.0
	Camphor	2.0	
C. Mercurial			
	Merthiolate	1-10,000	1-1,000
	Metaphen	1-20,000	
	Phenylmercuric Borate	1-100,000	1-15,000
D. Inorganic			
	Sodium Bisulfite	0.1	0.3
	Sulfurous Acid	0.06	
	Acetone Sod. Bisulfite	0.4	

Goldstein (7) has recommended concentrations of preservatives for use in ophthalmic preparations, which are, for the most part, applicable in parenterals and comparable to those concentrations listed in Table 1. However, he suggests a 1-20,000 concentration of Merthiolate and, in addition, lists benzalkonium chloride 1-5000, methylparaben 0.18% plus propylparaben 0.02% and phenylethyl alcohol 0.5%.

Several tests have been given to some of these preservatives and, although most workers have found that they are all bacteriostatic in recommended concentrations under proper conditions, Dove (8) presents the following preservatives in order of their decreasing germicidal activity:

Germicides in order of decreasing activity

0.001%	phenylmercuric nitrate
0.5%	chlorobutanol
0.05%	parachlorometacresol
0.5%	phenol
5 ppm	copper sulfate
0.2%	methyl parahydroxybenzoate

One should remember that the specific organism present, the pH of the solution, the concentration of agent used, and the medium used are all important factors in determining the most desirable agent for a particular preparation.

Babibbo and Godley (9) made limited tests for irritability of several different preservatives after autoclaving and gave these results as reactions on intradermal tests in 14 patients:

Number of reactions on intradermal test

6—0.5% chlorobutanol
4—0.5% phenol
2—0.04% mixture of methylparaben and propylparaben
2—saline control

On this basis they have used the parabens in practical work and claim that they are satisfactory from both a therapeutic and a pharmaceutical standpoint. Several things should be brought to mind when

reviewing this test, i.e., that the test was performed on only 14 patients, that the concentration of the parabens was fairly low compared to what is usually recommended for bacteriostatic activity, and that chlorobutanol on autoclaving decomposes liberating hydrochloric acid, which would be irritating.

Tests for incompatibilities with different medications were made by McEwan and Macmorron (10) who found that phenylmercuric nitrate gave the fewest difficulties (perhaps because of the small concentration—0.002%, chlorobutanol was next with most of the reactions being a "salting out" effect, and chlorocresol was found to be the most incompatible of all agents tested. The order of these preservatives tested, going from the most compatible to the least compatible, is:

phenylmercuric nitrate
chlorobutanol
phenol
cresol
chlorocresol

The parabens were not studied by these authors, but Gershenfeld (18) claims that the parabens do have incompatibilities. Few are listed in the literature other than the fact that iron is incompatible with phenolic compounds.

The exact mechanism of action of various preservatives is controversial and not too well understood. MacDonald (33) claims that the parabens block essential enzyme systems of organisms and prevent normal metabolism. Babibbo (9) states that the cationic quaternary ammonium compounds act by forming complexes with the electronegative bacteria.

The bactericidal activity of many compounds has been seriously questioned. That bactericidal activity of quaternary ammonium compounds can be reversed by relatively harmless surface cations, by high molecular anions, and proteins has been established by Valko and DuBois (11). Flett *et al.* (12) review the revival of organisms presumedly dead after treatment with mercury bichloride, sodium hypochlorite, and acriflavine, and then go on and show that *Staphylococcus aureus* and *E. typhosa* can be revived after treatment with dilutions of phenol (up to 1:65 for periods of time heretofore considered fatal) by adding either charcoal (physical inactivator) or

0.003% ferric chloride (chemical inactivator), the inactivators being added to the broth used for subculturing. The British process of sterilization by heating with a bactericide has been attacked (13), one author reporting that bacterial spores may survive heating with chlorocresol and that the method is not as efficient as autoclaving. However, it should be remembered, that usually none of the agents used is considered bactericidal in the concentrations recommended, but merely bacteriostatic. That is, they render the bacteria inactive and therefore prevent multiplication (9). This may be eventually fatal to the organism if the solution is not further contaminated, because most organisms cannot lie dormant in such a solution for an extended period of time.

The use of various preservatives and their effect on specific medications has received the attention of many, some of the most important reports are included below.

The drug or chemical receiving the most attention is penicillin. This is because penicillin is a potent, widely used antibiotic. It seems to be difficult to find a preservative which does not increase the rate of decomposition of the active ingredient or permit the development of color during the life of the product (14). Pencillin, an antibiotic, needs a preservative because it is effective only against most Gram-positive and a certain few Gram-negative organisms. Severe infections caused by injecting penicillin contaminated with *E. coli* or a fungus have occurred. Some of the wide-spectrum antibiotics are considered excellent bacteriostatics, even up to 1-1,000,000 dilutions, but the FDA has not allowed any antibiotic to be used as a bacteriostatic. Phenol is one of the most widely used bacteriostatic agents in penicillin solutions. Johnson and Lerrigo (15) have stated that chlorocresol (0.1%) causes turbidity and, although it seems to slow the loss of potency, it shows a heavy deposit in 24 hours (hence cannot be used), whereas phenol did not show turbidity after seven days had passed (the saline control showed no turbidity at all in the test period). Johnson and Lerrigo also claimed that the parabens and 2.0% phenoxital were compatible with the penicillin solution without affecting the stability, but they did not pursue the subject further.

Swollen (16) advocates the use of Versene (one of the salts of ethylenediamine tetra-acetic acid; Irgalon, or Sequestrene) along with a quaternary ammonium compound (Bradosol, or β-phenoxy-

ethyl-dimethyl-dodecyl-ammonium bromide) to stabilize aqueous penicillin solutions. One might question whether or not the penicillin might be inactivated by the quaternary agent and vice versa. The Versene acts as a chelating agent tying up trace metals which may be present and which may cause rupture of the penicillin ring structure. From his experiments, Swollen declares that penicillin solutions stabilized with Versene and Bradosol showed 98% potency after 35 days storage at 4 degrees C., while solutions preserved with phenol alone showed only 9.4% of original potency after the same period of time. After 14 days storage at room temperature the penicillin solution stabilized with Versene and Bradosol showed 78.2% potency while the control with phenol was only 52.2% of the original potency. Swollen reports in the same paper that Versene is a desirable agent to prevent oxidation of ascorbic acid.

Ascorbic acid solutions are somewhat unstable unless prepared carefully. The use of Versene with these was briefly mentioned above and will be discussed later in this paper. An article in The Bulletin of the American Society of Hospital Pharmacists (17) points out that since chlorobutanol reacts with ascorbic acid to form a biologically inactive compound, it is not a suitable antiseptic for ascorbic acid solutions. Phenol or the methyl and propyl esters of p-hydroxybenzoic acid are recommended.

The use of preservatives in procaine hydrochloride solutions was discussed by Babibbo and Godley (9). They noted that when using 0.5% phenol in procaine hydrochloride solutions the solutions became discolored after autoclaving. Other preservatives were tried and the results of these tests were:

Formation of color in procaine hydrochloride solutions:

preservative used	*degree of color*
unpreserved	1
parabens	1
phenol	111
chlorobutanol	colorless

From these results they decided that chlorobutanol seemed to have an antoxidant effect as well as a bacteriostatic effect. The validity of these results may be questioned because procaine hydrochloride solutions need to be buffered to a pH of about 3 to be stable, and

chlorobutanol decomposes on autoclaving releasing hydrochloric acid, lowering the pH. Thus, chlorobutanol may merely supply the proper pH for the procaine solution. Whether or not there is enough chlorobutanol remaining in the solution to act as an effective bacteriostatic agent is questionable.

Chlorobutanol and the parabens are unsuitable for use in serums because these preservatives require either heating or vigorous shaking to effect solution. Neither procedure is recommended for serums because of the possibility of denaturation of the protein. It is recommended that a potent agent which can be added in a small quantity (such as phenylmercuric nitrate, Merthiolate, or phenol) be used. Phenol and cresol are quite popular and effective here but they may cause "smarting" and pain on injection. Merthiolate is extremely popular in the United States (see list of representative proprietaries several pages hence). The quaternaries are unsuitable because of ease of inactivation by serum.

Gershenfeld (18) points out that there is no definition of bacteriostatic agents in the present U. S. P. XIV, however, the U. S. P. XII and XIII stated that they "must prevent the growth and development of all micro-organisms." It might well be noted that the U. S. P. and N. F. do not use the word "bactericide" as a preservative.

The United States Pharmacopeia (19) and the National Formulary (20) state the following:

Added substances, U. S. P. XIV, p. 5, N. F. IX, p. 8.

"For the preservation of solutions of organic substances intended for parenteral administration or topical application, in addition to Injections, there may be present in the solutions, unless otherwise directed in the monograph, not more than 0.5 per cent of chlorobutanol, cresol, phenol, or other suitable preservative, and, in addition, not more than 0.2 per cent of sulfur dioxide or its equivalent of sodium bisulfite or sodium sulfite. Not more than 0.9 per cent of sodium chloride may be present, and the air in the container may be evacuated or be replaced by carbon dioxide, or by nitrogen.

"Substances, unless otherwise provided in the individual monograph, may be added to pharmacopoeial preparations to assure the permanency or usefulness of the products, but these substances must be non-toxic and harmless in the amounts ad-

ministered and must not interfere with the therapeutic efficacy of the preparation.

"The presence and proportion of such preservative or other added substances shall be plainly declared on the label of the container in which the product is sold or dispensed."

To quote further from U. S. P. XIV, p. 725.

"Special care must be observed in the choice and usage of added substances in Injections which are administered in volumes exceeding 5 cc.

"A suitable substance or mixture of substances to prevent the growth of micro-organisms must be added to Injections packaged in multiple-dose containers, regardless of the method of sterilization employed, unless otherwise directed in an individual monograph.

"Such substances, if added, must be used in concentrations which will prevent the growth of all micro-organisms in the Injection. Sterilization processes must be employed even though such substances are used."

The United States Dispensatory (21) states about the same thing but mentions the use of preservatives in single dose packages.

Added substances, U. S. D., p. 562.

". . . A bacteriostatic agent may be added to Injections packaged in single-dose containers and prepared by *Aseptic Manipulation*, or by *Bacteriological Filtration* (*Process F*), or, in emergencies, by a procedure in which only one exposure at 100 degrees is used in *Fractional Moist-Heat Sterilization* (*Process* E). If bacteriostatic agents are added, they must be used in concentrations which will prevent the growth of all bacteria in the Injections, and sterilization processes or aseptic manipulation must be employed even though bacteriostatic agents are used."

The use of bacteriostatics in single dose vials is advocated as a safety precaution, so that in case of contamination, these bacteriostatics not only prevent multiplication of the bacteria, but in about 30 days are fatal to the bacteria and eventually may even be fatal to spores.

The British Pharmacopoeia endorses a method of sterilization with a bactericide:

The British Pharmacopoeia, 1948, p. 828.

"Process 3. Sterilisation by Heating with Bactericide."

"The solution is prepared by dissolving or suspending the medication in a 0.2% w/v solution of chlorocresol in Water for Injection or in a 0.002% w/v solution of phenylmercuric nitrate in Water for Injection. The solution or suspension of the medicament is distributed in the final containers which are then finally sealed. When the volume in each container does not exceed 30 ml. the contents are heated at 98 to 100 degrees C. for thirty minutes. When the volume in each container exceeds 30 ml. the containers are heated for a longer time, sufficient to ensure that the whole of the solution or preparation is maintained at the temperature of 98 to 100 degrees for thirty minutes.

"Solutions of medicaments to be used for intravenous injection shall not be prepared by this method when a single dose of the injection is greater than 15 mg. Solutions of medicaments to be used by intrathecal, intracisternal, or peridural injection shall not be prepared by this method.

"When the container is sealed so as to permit the withdrawal of successive doses on different occasions, the solution or preparation of the drug contains a suitable bacteriostatic agent in such concentration as will prevent the growth of microorganisms.

"Suitable bacteriostatics are phenol 0.5%, cresol 0.3%, chlorbutol 0.5%, chlorocresol 0.1% and phenylmercuric nitrate 0.001%. A bacteriostatic need not be added if the medicament itself has sufficient bacteriostatic power. The bacteriostatic used should not interfere with the therapeutic efficacy of the drug nor cause a turbidity in aqueous solutions of the drug."

As stated before, Davis and Davison (13) found that this method is not bactericidal nor is it as efficient a method as autoclaving.

A list is presented giving some typical proprietary products and the preservative used (see Table 2).

TABLE 2

REPRESENTATIVE PROPRIETARY PRODUCTS AND PRESERVATIVES USED

Product	*Preservative*
Synkavite Sod. Diphosphate	sod. metabisulfite & 0.45% phenol
Menadione in Oil	0.5% cresol
Sod. Ascorbate Inj.	0.35% chlorobutanol
" " "	0.01% aminoacetic acid
" " "	0.1% sod. bisulfite
" " "	0.5% chlorobutanol & 0.1% sod. bisulfite
" " "	equivalent of 0.08% sulfurous acid
Vitamin B_{12}	2.0% benzyl alcohol
" "	0.5% phenol
Bevidox Crystalline	0.01% benzethonium chloride
Tubocurarine Chloride	0.5% chlorobutanol
" "	0.9% benzyl alcohol
Metubine Iodide	0.5% phenol
Intocostrin	0.5% chlorobutanol
Testosterone Propionate in Oil	1-50,000 phenylmercuric borate
Testosterone Propionate in Oil	0.5% chlorobutanol
Testosterone Propionate with 3% benzyl alcohol	0.1% propylparaben
Testosterone Propionate aqueous suspension	1-10,000 thimerosal
Korotrin	0.2% cresol
Lyovac Chorionic Gonadotropin	0.35% phenol
Entromone	0.4% phenol
Chorionic Gonadotropin	0.5% chlorobutanol
Lyophilized Chorionic Gonadotropin	0.5% phenol
Corticotropin	0.5% phenol
Progesterone Aqueous	1-10,000 thimerosal
Progesterone in Oil	0.5% chlorobutanol
" " "	0.004% phenylmercuric benzoate
Proluton	0.1% propylparaben

Product	*Preservative*
Prometron	0.1% propylparaben
Cyclogesterin	0.5% chlorobutanol
Depo-Testosterone	0.5% chlorobutanol
Diethylstilbestrol Dipropionate in Oil	0.5% chlorobutanol
Procaine Hydrochloride	0.01% sod. formaldehyde sulfoxalate
Theelin Suspension	1-10,000 benzethonium chloride
Mercuhydrin Sod.	0.18% methylparaben & 0.02% propylparaben
Veriloid Solution	0.5% chlorobutanol
Heparin Sodium	1-10,000 thimerosal
" "	0.5% chlorobutanol
" "	0.5% phenol
" "	0.45% phenol
" "	0.18% methylparaben & 0.02% propylparaben
Blood Group Specific Substances A & B	0.3% phenol
Tuamine Sulfate 1%	1-50,000 phenylmercuric nitrate
Vonedrine HCl 2.8%	0.05% methylparaben & 0.01% propylparaben
Neostigmine Methyl Sulfate	0.18% methylparaben & 0.02% propylparaben
Dihydrostreptomycin Sulfate	0.9% benzyl alcohol
Dihydrostreptomycin Sulfate	0.25% phenol
Procaine Penicillin G Aqueous Suspension	0.18% methylparaben & 0.02% propylparaben
Procaine Penicillin G	0.015% butyl p-hydroxybenzoate
Crysticillin Aqueous	0.13% methylparaben & 0.015% propylparaben
Xylocaine	0.1% methylparaben
Methadone HCl	0.5% chlorobutanol
" "	0.9% benzyl alcohol
Chlor-Trimeton Maleate	1-10,000 thimerosal
Tri-Immunol	1-10,000 sod. ethylmercurithiosalicylate (thimerosal)

Product	*Preservative*
Priscoline	0.5% chlorobutanol
Gas Gangrene Antitoxin	0.4% phenol & 1-20,000 phenylmercuric borate
Benadryl	1-10,000 Phemerol
Intraheptol	0.45% phenol
Dramamine	5% benzyl alcohol
Influenza Virus Vaccine	1-10,000 Merthiolate
Adrenalin	0.5% Chloretone & 0.1% sod. bisulfite
Depropanex	0.25% phenol
Cortisone	1-10,000 sod. ethyl mercurithiosalicylate
Efocaine	1-25,000 phenylmercuric borate & 0.1% sod. metabisulfite
Cortate	0.1% propylparaben
Adrenal Cortex Extract	10% alcohol
Nydrazid	0.5% Chlortone
Nicamin	0.9% benzyl alcohol
Metrazol	0.2% paraben esters
Neo-Synephrine	0.5% chlorobutanol
Pronestyl	0.9% benzyl alcohol & 0.04% sod. bisulfite
Pyridoxine	0.5% phenol
Quinidine Gluconate	0.25% phenol & 1% monothioglycerol
Picrotoxin	0.9% benzyl alcohol
Solganol in Oil	0.1% propylparaben
Etamon Chloride	1-20,000 Phemerol

Most immunologic agents accepted by the N. N. R. are preserved with 1-10,000 thimerosal; the following are two of the exceptions:

Combined Diphtheria-Tetanus Toxoid	benethonium chloride 1-10,000
Anti-Hemophilus Influenza Type B Serum	1-10,000 thimerosal and 0.2% phenol

We shall now discuss briefly the most important preservatives used in parenteral solutions.

A. Phenolic Group

1. Phenol U. S. P., B. P.
   (Carbolic Acid; soluble in water 1-13)
2. Cresol U. S. P., B. P.
   (Tricresol; soluble in water 1-50)
3. Chlorocresol B. P.
   (Parachlorometacresol; soluble in water 1-250)
4. Chloroxylenol
   (Parachlorometaxylenol, PCMX)
5. Parabens
   Considered under a separate heading

Phenol and cresol are widely used and considered the most popular preservatives (3, 18) because their bacteriostatic activity is little influenced by serum and they are not easy to inactivate (3, 18, 21). Odor, color, and production of sensitivities are their main objectionable features (18).

Generally, 0.5% phenol and 0.3 to 0.5% cresol are used (3, 23) against non-sporulating organisms; 0.5% phenol and 0.3% cresol being considered to have the same activity. In penicillin injections these produced no turbidity for a week, whereas chlorocresol does produce some turbidity within that time. In another paper, 0.1% cresol is claimed to have the same toxicity as phenol, but to have 10 times the bacteriostatic power. Since 0.05% cresol is equivalent to 0.5% phenol as a bacteriostatic (note disagreement with an above statement), 0.1% cresol has a greater margin of safety than 0.5% phenol (3). For antisepsis, the U. S. D. (21) states that the meta isomer of cresol is best, the ortho weakest. The meta isomer is the least toxic.

It is claimed (21) that phenol is active in 1-800 dilution (0.125%) and inhibits multiplication of bacteria but does not kill spores. Phenol and cresol are incompatible with iron; cresol is also incompatible with alkaloids, acting as an alkaloidal precipitant.

Chlorocresol and chloroxylenol are used in Great Britain, chlorocresol being recognized by the British Pharmacopoeia for use in the process "Sterilisation by Heating with a Bactericide" (21, 24) in 0.1 to 0.25% concentrations (22, 23, 24, 25). It is claimed that chlorocresol is a stronger antibacterial agent than either phenol or cresol

(21), the para isomer (the isomer recognized as "official") being more active than the meta isomer. Organic material lowers its efficiency. Wein (24) advocates replacing 0.5% phenol with 0.25% to 0.3% parachlorometacresol or 0.002% phenylmercuric nitrate, claiming that *p*-chloro-*m*-cresol has the same toxicity as phenol but can be used in smaller amounts.

Chlorocresol is stable to heat and light, its activity is unchanged after autoclaving and storage (25) but is said to be more active in acid solutions than in alkaline solutions (23). It has little toxicity, nevertheless, it should be restricted so that only small intermittent doses are injected. It should not be used in intraspinal injections or when the intravenous dose exceeds 15 mg.

Solutions of chlorocresol are incompatible with penicillin, codeine phosphate, papaverine, ergotinine citrate, aneurine, hydrated calcium chloride, carbachol, diamorphine hydrochloride, digitalin, ergometrine, homatropine hydrobromide, physostigmine salicylate, quinidine hydrochloride, sodium cacodylate, sodium chloride, sodium glycerophosphate, sodium morrhuate and strychnine hydrochloride (3, 10, 23). It has been reported that 0.1% and 0.05% solutions of chlorocresol cause hemolysis (3).

Chloroxylenol is said to have two times the activity of chlorocresol but it has a very low solubility and is seldom used except in external fatty preparations (3). Lum (26) points out that chloroxylenol in 0.35% concentration is much more efficient than 0.5% phenol as a preservative.

B. Parahydroxybenzoates

1. Methylparaben U. S. P.
   (methyl parahydroxybenzoate, Methyl Parasept, Solbrol, Tergosept M, Nipagin M)
2. Ethyl p-hydroxybenzoate
3. Propylparaben U. S. P.
   (propylparahydroxybenzoate, Propyl Parasept, Tergosept P)
4. Butyl *p*-hydroxybenzoate
   (Butoben)
5. Benzyl p-hydroxybenzoate

These are colorless, neutral, relatively non-toxic, non-volatile, slightly soluble, stable chemicals effective in low concentrations against

a diverse number of micro-organisms in acid, alkaline, or neutral solutions (*27*, *28*, *33*). They are odorless and tasteless except in saturated aqueous solutions when they have a slight tang or cause a burning sensation. In alkaline solutions above a pH of 8.0 they hydrolize to a small extent; however, at pH 3 to 6 they show no decomposition when heated for two hours at 100° C. or for 30 minutes at 120° C. (*28*). Higher concentrations are needed in oil products and emulsions than in aqueous solutions.

The parabens are essentially non-toxic requiring huge doses to kill. They are considered safe, practically non-irritating, and non-allergic; they seem to be excreted rapidly in a conjugated form (*29*).

The parabens were first used in 1924 and recognized in the Swiss Pharmacopoeia in 1934. They are not widely used in Great Britain as bacteriostatics but are extremely popular in the United States where many papers about them have been published.

The parabens are efficient anti-fungal agents, the activity increasing with larger alkyl groups (*27*, *29*). Greater concentrations are needed to inhibit bacteria and they are more active against Gram-positive organisms than Gram-negative. In the Gram-negative class there is not the increase in efficiency of bacteriostasis with increase in alkyl chain (*29*).

Some essential information on the concentration of parabens needed, phenol coefficients, solubilities, etc., are given in Table 3.

TABLE 3

DATA ON PARABENS

ester	.phenol coef. (33)	.min. conc. ester needed for most resistant bact. (30)	solubility 20-30 min. shaking at 25°C.	solubility 25°C.	solubility 80°C.	.alcohol	recommend .conc. for aqueous sol'n (31)
Methyl	3	0.125%	0.15%	0.25%	2.0%	52%	0.15%
Ethyl	8	0.15%	0.10%	0.17%	0.86%	70%	0.05%
Propyl	17	0.15%	0.03%	0.05%	0.30%	95%	0.02%
Butyl	32	0.15%	0.015%	0.02%	0.015%	210%	0.01%
Benzyl	80						0.01%

It will be noticed that the recommended concentrations fall within that concentration soluble by shaking for 20 to 30 minutes, but higher concentrations than are actually soluble are required of

the higher esters to inhibit the most resistant bacteria (usually Gram-negative organisms). The ethyl, propyl and butyl paraben esters in a concentration of 0.15% inhibited growth of typically resistant bacteria in both acid (pH 3-4) and alkaline (pH 7-8) gelatin solutions but the methyl ester was only partially effective (*27*). The methyl ester is highly recommended for inhibiting mold growth and the propyl ester for inhibiting yeast (*21*).

Most workers recommend that a combination of esters be used for preventing growth of bacteria (*18, 27, 32, 33*), two are generally used where increased activity and higher concentrations are needed; and three or more esters in combination are more active and more soluble than an equal amount of a lower ester alone. The combination of 0.18% methyl ester and 0.02% propyl ester is the most often recommended being advocated for ascorbic acid injection (*27*) where the stability and neutral reaction of the parabens are advantageous. In sodium penicillin G aqueous solution and procaine penicillin aqueous suspension, this combination acts as both an antibacterial and antifungal agent (*15, 27, 32*). In fact, recent use of this concentration of parabens has been advocated to prevent development of moniliasis during antibiotic therapy.

Because of the limited solubility, several papers have been published concerning the incorporation of the esters into aqueous solution. Aalto, *et al.* (*27*) and the Heyden Chemical Corporation (*28*) suggest dissolving 2.5% propylparaben in ethanol and adding it slowly to 500 ml. water (0.04% final concentration), or 15% solution of methylparaben in ethanol added slowly to water to give a final concentration of 0.12%.

MacDonald (*33*) claims that the preservative action of the parabens is by blocking an enzyme system of the organism and preventing normal metabolism and growth.

C. Neutral Agents

1. Chlorobutanol U. S. P., Chlorbutol B. P. (Chloretone)

Chlorobutanol is by far the most important preservative in this group, being widely used both in this country and abroad. It is analgesic, non-toxic and a non-reactive antiseptic, has a phenol coefficient of 1.2 and is used in 0.5% concentration as a preservative

(3, 21). It is compatible with a large number of chemicals and drugs and is used extensively as a bacteriostatic in parenterals. Many multiple dose vial formulas recommend 0.5% chlorobutanol, even though some authors claim that if 0.5% is used filtration will remove a portion of the chlorobutanol (37). According to the literature, 0.8% (saturated solution) is completely bacteriostatic (35). The *Merck Index* (36) states that chlorobutanol is easily soluble in boiling water, however, Gershenfeld has shown (35) that chlorobutanol is decomposed at such high temperatures.

Although some authors recommend the use of chlorobutanol in multiple dose vials which are sterilized by Process D (moist heat, i.e., 100 degrees C. for 30 minutes for three days) (38), Gershenfeld (35) states that chlorobutanol decomposes at 65 degrees C. with the liberation of hydrochloric acid, and it also decomposes readily in alkaline solutions. He experimented with concentrations of 1-200 to 1-1,000 (0.5 to 0.1%) and found that in no instance did chlorobutanol display a bactericidal effect against test organisms and spores; and that 1-200 was the only dilution that displayed bacteriostatic action under all conditions employed except when heat was used. Sterilization by autoclaving destroyed the chlorobutanol quite completely; heating to 65 degrees C. for 30 minutes for three days gave the least amount of decomposition but still the pH decreased from 0.10 to 0.60 units. In all heated solutions (including the 1-200 concentration) growth was revealed.

Because of the limited solubility (0.8%) and the inability to heat the chlorobutanol without decomposing it, Schmetz (39) has listed several methods by which chlorobutanol can be put into solution:

a. add chlorobutanol to pint of water and shake for a few minutes every hour for 24 hours.

b. heat water to 60 degrees C. and add solute, shake as temperature falls to 40-45 degrees, otherwise chlorobutanol precipitates out at about 48 degrees.

c. dissolve in alcohol and add to water, at least 8% alcohol is needed.

Mixtures of chlorobutanol in Isotonic Sodium Chloride Solution are stable only if the percent does not exceed 0.5%; above 0.5% the chlorobutanol is "salted out."

2. Benzyl Alcohol N. F.

Benzyl alcohol, soluble 1-25, is added to many intramuscular injections in 2% concentration as a local anesthetic and preservative (32), Gershenfeld (40) found that 1% solutions and stronger were bacteriostatic against the test organisms and spores used. He found that benzyl alcohol, when given subcutaneously or intramuscularly undiluted caused irritation and necrosis (sterile), but that concentrations of 0.5 to 4.0% showed no irritation. A disadvantage in the use of benzyl alcohol is its "sting" (18).

D. Mercurials

1. Thimerosal N. F.
   (Merthiolate, thimersolate, sodium ethylmercurithiosalicylate)
2. Metaphen
3. Phenylmercuric Nitrate N. F., B. P. (Merfenil)
   Phenylmercuric Chloride N. F.
   Phenylmercuric Borate
   Phenylmercuric Acetate

Merthiolate (Thiomersalate—British) is a commercial product widely used as a bacteriostatic agent recommended in strengths ranging from 1-1,000 to 1-100,000 (6, 18, 23). It is stable only in neutral or alkaline solutions, thus, phenylmercuric nitrate, which is stable also in acid solutions, is sometimes recommended in its place (3).

The phenylmercuric salts, of which the nitrate is the most widely used, is mentioned in the British Pharmacopoeia for use in the process of "Sterilisation by Heating with a Bactericide." Phenylmercuric Nitrate is only slightly soluble in water (1-1250) but is a potent bacteriostatic agent, is compatible with acid or alkali, and is relatively non-toxic (3). Its activity is reduced in presence of body fluids (23). The acetate is more soluble (1-600) but has less bacteriostatic power, especially in solutions whose pH is above 7.2. The chloride and bromide are practically insoluble. This latter property makes halides incompatible with phenylmercuric nitrate.

The bacteriostatic efficiency of phenylmercuric nitrate is widely disputed by different authors. The *Extra Pharmacopoeia* (23) states

it is a strongly active bacteriostatic agent but less effective as a bactericide then mercuric bichloride (but also less toxic and less irritating) and is fungicidal in concentrations up to 1-30,000. Berry *et al.* (25) report that 0.001% phenylmercuric nitrate is impressive, being stable and active the full pH range with a low toxicity. Autoclaving and exposure in a window did not alter antibacterial power. Davison (41), by both dilution and filtration techniques and by heating the medication to 100° C. for 30 minutes with phenylmercuric nitrate (as suggested in the B. P.), showed that relatively low concentrations of spores survive the B. P. process of heating with a bactericide. The *United States Dispensatory* (21) reported that some workers claim that 1-120,000 dilutions are bacteriostatic while others claim that 1-1,500 dilutions are not. However, Gershenfeld had repeated success with 1-50,000 concentrations on long standing. He reported that it is inferior to mercuric chloride and does not kill spores.

In a series of tests on compatibilities of bacteriostatic agents, McEwan and Macmorron (10) reported that phenylmercuric nitrate gave the fewest reactions of all preservatives tested (perhaps because of the small concentration used—0.002%). This concentration has been suggested to replace 0.5% phenol (24) because of the low toxicity (about the same as merthiolate), which is unlikely to be harmful.

Phenylmercuric nitrate is incompatible with halides, homatropine hydrobromide, ergometrine and hyoscine hydrobromide (3). Solutions should be protected from light, and on standing they may deposit elemental mercury (23).

E. Miscellaneous Bacteriostatics

1. Benzoic Acid, Sodium Benzoate U. S. P.

According to Sokol (29), sodium benzoate is inferior to phenol, its activity falling off above pH 6.0. The U. S. D. (21) states that at pH 3.5 sodium benzoate is bacteriostatic in 1-1,000 concentration, but not bacteriostatic in the same concentration at pH 5.0.

2. Quaternary Ammonium Compounds

Although these substances are being used more and more, the literature does not contain many references to their use as preservatives in parenterals. Valko and DuBois (11) admit that they are bacteriostatic and may even be bactericidal on long standing, but

these authors then showed that these antiseptics can be easily inactivated by a variety of substances. Tice and Moore (42) showed that Ceepryn and Phemerol were both bacteriostatic in gelatin and sucrose solutions and that Ceepryn seemed to be the better of the two. Both of these compounds showed coacervation with Pharmagel B. It was mentioned before that protein (serum) and large molecular anions inactivate these compounds.

Phemerol (or benzethonium), a quaternary ammonium compound, is mentioned several times in the list of proprietary medications as the bacteriostatic agent. Zephiran (benzalkonium) could conceivably be used also.

3. Boric Acid

Boric acid is considered toxic (causes hemolysis of the red blood cells in all concentrations) and is never used for parenteral solution. Nevertheless, one author (43) claims that in concentrations of from 0.5 to 1.5% in injections, it showed no toxic effects on cats and dogs.

4. Phenylethyl Alcohol

Phenylethyl alcohol is little used for injections. It is more widely used for ophthalmic preparations. It is interesting to report that Lilley and Brewer (44) showed that this agent exerts a greater bactericidal effect against Gram-negative organisms than against Gram-positive.

5. Oleaginous preparations

Gershenfeld (18) recommends 2% benzyl alcohol or 4% chlorobutanol for the preservation of oleaginous preparations. The higher parabens, especially propylparaben, are used somewhat commercially. A recent report (48) shows that there is no good sporicidal preservative for either hydrous or anhydrous oleaginous preparations. Under hydrous conditions, both Merthiolate, 1-50,000, and benzyl alcohol, 2%, destroyed non-sporulating organisms in eight days, but were ineffective against spores. Under anhydrous conditions, selecting the third day as an arbitrary basis for evaluating sporicidal activity, catechol 1.0%, hexylresorcinol 0.5%, carvacrol 1.0% and epichlorhydrin 1.0% showed effectiveness; propyl-*p*-hydroxybenzoate 1.0%, chlorobutanol 5.0% and benzyl alcohol below concentrations of 2.0% were the least effective. Phenol 2% required 10 days to produce sporicidal effectiveness, phenylmercuric nitrate was not yet com-

pletely sporicidal after 13 days. In the same paper, in a series of commercial products, the only one showing sporicidal activity after 14 days was one containing 3% benzyl alcohol. The validity of this result is questionable because in the same test series a product containing 0.1% propyl paraben and 3.0% benzyl alcohol did not show sporicidal activity in that time limit (14 days).

6. Movidin

Movidin is a silver compound which was mentioned at the annual meeting of the Parenteral Drug Association in 1953. Movidin is not available for general use nor is there much information available on the compound, especially for use as a preservative in parenterals.

It is difficult or impossible to say just which bacteriostatic preservative is the best. Phenol and cresol are certainly useful and applicable in most all injections. The parabens and chlorobutanol are somewhat more potent and can be used almost interchangeably except when the solution need be heated, and here the parabens have the advantage. Phenylmercuric nitrate, thimerosal, phenol, or cresol seem to be the preservatives most useful in sera and biological products.

All in all, no one preservative is totally satisfactory in that it meets all the requisites of the ideal.

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SELECTED ABSTRACTS

A Vehicle for Intrapleural Injections. Seal, K. S., *Pharm. J. 170*:475 (1953). The effectiveness of streptomycin and dihydrostreptomycin in the treatment of tuberculous empyema has been less than that in most other types of tuberculosis because of the difficulty in obtaining sufficient penetration of the antibiotics into the pleural cavity. Streptomycin is particularly difficult to obtain in therapeutic levels in the pleural fluid.

Based upon previously reported work, a formula was developed for a vehicle for dihydrostreptomycin for intrapleural injection. An attempt was made to prepare a solution having a pH of 7.8, the pH at which dihydrostreptomycin appears to be most effective, and a viscosity of 5 to 8 cps. This solution is intended to be injected into the pleural capacity after the cavity has been washed with sterile saline.

The following formula was developed as being satisfactory:

Sodium carboxymethylcellulose	1.0	Gm.
Disodium phosphate .12 H_2O	3.366	Gm.
Methyl parahydroxybenzoate	0.1	Gm.
Distilled Water to make	100.0	cc.

The freshly distilled water is heated to boiling and the disodium phosphate and the preservative are dissolved in 90 cc. The solution is filtered and SCM, previously heated for 1 hour at 100° C., is sprinkled on the surface of the solution and agitated by means of a mechanical stirrer. The solution is then brought up to volume, 300 cc. filled into bottles, and autoclaved at 120° C. for one-half hour. Immediately before use one gram of dihydrostreptomycin is added to each bottle. The addition of the antibiotic lowered the pH slightly, the average final pH being about 7.76.

The author discussed various problems encountered in developing this formula and in determining the most effective means of sterilization. The vehicle as described had been used for some time and had proven to be satisfactory and without undesired side effects.

Observations on the Spread of Antibiotic-Resistant Staphylococci. Dowling, H. F., Lepper, M. H., and Jackson, G. G. *Am. J. Pub. Health 43*:860 (1953). Recent reports had indicated that from 37 to 70 per cent of hospitalized patients carry penicillin resistant staphylococci. The authors felt that it was important to gain some epidemiological information as to the fate of these organisms after the patient returns home. Considerable information has been reported concerning the acquiring of such organisms while a patient is in a hospital and the development of resistant strains during antibiotic therapy, but little information has been forthcoming concerning the giving and acquiring of resistant strains in the community from symptom-free carriers.

Nose and throat cultures, totaling 191, were taken from 54 patients before and for 8 to 21 weeks after their discharge from a contagious disease hospital. A total of 1,213 cultures were also taken from the 209 household contacts of these patients. The staphylococci present were studied with respect to their biological characteristics, their sensitivity to penicillin and aureomycin, and were typed by the bacteriophage method wherever possible.

Staphylococci were found in 74 per cent of the cultures taken from the patient at the time of discharge from the hospital, but only 36 per cent showed the organisms after 4 weeks. Household contacts showed about 33 per cent of the cultures with staphylococci. Of the staphylococci obtained 1 or more units of penicillin per cc. were required for inhibition in the cultures from 85 per cent of hospital personnel, 88 per cent of the patients at discharge, 36 per cent after 4 weeks, and 30 per cent in household contacts. With aureomycin, 10 or more micrograms were required for inhibition in the cultures from 64 per cent, 78 per cent, 14 per cent, and 7 per cent, respectively.

A transfer of strains of staphylococci to one or more of the household contacts was found to occur from the nose or throat of 13 per cent of the patients observed. However, there was no significant increase in the carrier rate of resistant strains among household contacts after the arrival of patients in the household. After the seventh week there was no significant increase in the carrier rate among the patients, either, although the carrier rate for resistant strains among the patients for the first few weeks following discharge from the hospital was much higher than that for the population at large.

BOOK REVIEWS

The Pharm-Assist Manual. By A. E. Slesser, Professor of Pharmacy, University of Kentucky College of Pharmacy. The C. V. Mosby Company, St. Louis, 1953. Pp. 167 incl. index. Price $3.50.

The Pharm-Assist Manual is a small volume containing a wide variety of information in concise form. Its contents, too numerous to be listed, are sufficiently diverse to make the book a useful review-reference for students or practitioners of pharmacy and the allied health sciences.

The book is probably of most value to the busy pharmacist. He may wish to look up the meaning of some medical term or clarify in his mind the difference between the various classes of autonomic drugs such as sympathomimetics and parasympatholytics. He can find the use of any official organic drug in neat tabular form. (This is especially helpful since the USP and NF do not list therapeutic uses.) In an emergency he may look up the antidote for the common poisons. Or, at his leisure, he may wish to browse and refresh his memory of basic inorganic or organic chemistry.

The Manual has several sections devoted to definitions: of pharmaceutical terms and processes, of organic chemical terms, of bacteriologic terms, and of therapeutic terms. Having these definitions at one's fingertips without needing to delve through the indices of cumbersome textbooks will prove extremely helpful. The condensed nature of the definitions leads to a regrettable vagueness in a very few instances: *emulsion* and *sterol*, for example. For the most part, however, the definitions are excellent.

One of the five Parts of this book is devoted to pharmaceutical calculations. The discussion (supplemented by sample problems) shares the lucidity which characterizes the entire volume.

In conclusion, a word must be said in praise of Dr. Slesser's sections on General Compounding Considerations, Common Compounding Problems, and Prescription Incompatibilities. In the first of these sections, particularly, the essence of prescription compounding has been presented in highly concentrated, yet crystal-clear form. Teachers of Dispensing Pharmacy will enjoy, and students will profit from, a perusal of this portion of the *Pharm-Assist Manual*.

STANLEY SCHEINDLIN

Veterinary Dermatology. By Frank Kral and Benjamin Novak. J. B. Lippincott Company, Philadelphia, 1953. Illustrated. 325 pp. 17.5 x 25.5 cm. Price $10.00.

Veterinary literature has been greatly enriched with the appearance of the first text on Veterinary Dermatology in the English language. There has long been a great need for a reliable text on the cutaneous diseases of animals.

The first book on skin diseases in animals was *Hautkrankheiten bei Haustieren* by Schindelka, published in Vienna in 1908. The second was *Veterinarni Dermatologie* by Kral, published at Brno, Czechoslovakia in 1931.

Although Dr. Kral's earlier book served as the basis for the new text, it is not a mere translation. The senior author has been in the United States five years, but this work contains many new American proprietaries, in addition to numerous prescriptions of field-tested value. Dr. Kral's many years of experience have also provided 162 excellent and well selected photographs, which are by far the book's most outstanding feature.

Every phase of dermatology is covered, including a basic survey, examination of the skin, and causes and classifications of skin disorders. Also discussed in detail are dermatitis, otitis externa in dogs, and skin manifestations in the course of infectious diseases caused by viruses, by bacteria, by fungi, and by protozoa.

Many special topics are discussed, such as eczema, drug eruptions, food rashes, photosensitization, skin tumors, and three comprehensive chapters on dermatoses associated with metazoan parasites. Presentation of etiology, symptomatology, prognosis and treatment is orderly, and each of the twenty-one chapters is followed by a complete bibliography.

The book is to be translated into German, Spanish and Yugoslavian in the near future.

The senior author's vibrant personality is evident throughout the book. As many dermatological afflictions are transmissible from animal to man, this publication is highly recommended, not only to the veterinarian, but to the practitioner of human dermatology as well.

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The American Journal of Pharmacy is the oldest continuously published scientific periodical of its kind in America, having been established by the Philadelphia College of Pharmacy in 1825. After the original issue there were three other preliminary numbers until 1829, when regular publication began. From then until 1852 four issues were published annually, with the single exception of 1847, when an additional number appeared. Six issues a year were printed from 1853 to 1870, at which time the Journal became a monthly publication.

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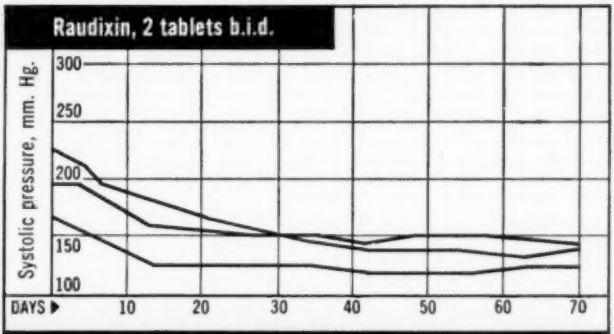

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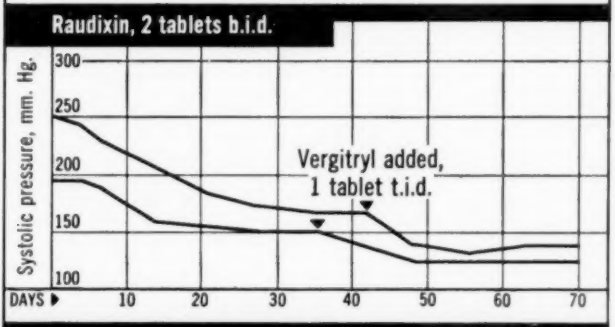

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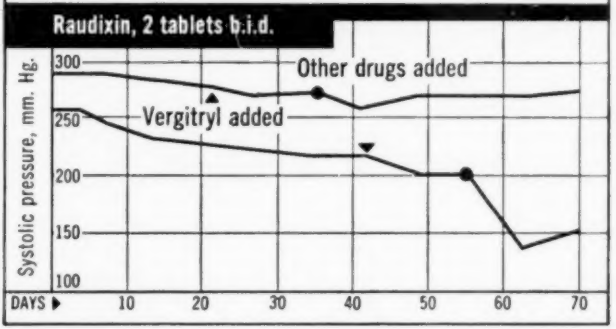

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